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REMARKS / ARGUMENTS

Claims 22-25 and 27-37 were pending in this application. In the instant correspondence, Applicants have amended claims 22, 28, and 33 (without prejudice to prosecuting the original claims as filed, or claims similar thereto, in subsequently filed applications). Claims 22-25 and 27-37 remain pending after entry of the amendment to the claims in the instant correspondence. Claims 22-25 and 27-37 were rejected. The Examiner made the following rejections:

A. Anticipation

1. The Examiner rejects, under 35 U.S.C. § 102(e), claims 22-25 and claims 27-37 as being anticipated by Gosselin et al. (U.S. Patent 5,789,441; priority to February 15, 1996).
2. The Examiner rejects, under 35 U.S.C. § 102(b), claims 22, 23, 27-29, 32-34, and 37 as being anticipated by Imai et al. (1990; Jpn J. Allerg. 39 (10):1380-1387).
3. The Examiner rejects, under 35 U.S.C. § 102(b), claims 22, 23, 27-29, and 32 as being anticipated by Martin et al. (1989; J. Clin. Invest. 84: 1609-1619).
4. The Examiner rejects, under 35 U.S.C. § 102(b), claims 22, 23, 27-29, and 32 as being anticipated by Johnson et al. (1991; Agents and Action 33(3/4): 260-271)."
5. The Examiner rejects, under 35 U.S.C. § 102(b), claims 22, 24, 25, 27, 28, 30-33 and 35-37 as being anticipated by Fujimura et al. (1991; Prostaglandins 42(4):379-389).
6. The Examiner rejects, under 35 U.S.C. § 102(b), claims 22, 24, 25, 27, 28, 30-33, and 35-37 as being anticipated by Ludwig et al. (1998; J. Appl. Physiol. 65(3): 1424-1429).
7. The Examiner rejects, under 35 U.S.C. § 102(b), claims 22, 24, 25, 27, 33, and 35-37 as being anticipated by Ball et al. (1991; J. Pharmacol. Methods 26: 187-202).

8. The Examiner rejects, under 35 U.S.C. § 102(b), claims 22, 23, 27-29, and 32 as being anticipated by Johnson et al. (1985; Prostaglandins 29(2):313-322).
9. The Examiner rejects, under 35 U.S.C. § 102(b), claims 22, 24, 25, 27, 28, 30-33 and 35-37 as being anticipated by O'Donnell et al. (Agents and Actions 14(1): 43-48 (1984))

B. Obviousness

11. The Examiner rejects, under 35 U.S.C. § 103(a), claims 22-25, and 27-37 as being unpatentable over Gosselin et al. (U.S. Patent 5,789,441; priority to February 15, 1996) in view of Fujimura et al. (1991; Prostaglandins 42(4):379-389).
12. The Examiner rejects, under 35 U.S.C. § 103(a), claims 22-25, and 27-37 as being unpatentable over Gosselin et al. (U.S. Patent 5,789,441; priority to February 15, 1996) in view of Ludwig et al. (1998; J. Appl. Physiol. 65(3): 1424-1429).

The Applicants believe the present amendments and the following remarks traverse the Examiner's rejection of the pending claims. These remarks are presented in the same order as they appear above.

A. The Claims Are Not Anticipated

It is well settled law that, under 35 U.S.C. §102, anticipation, "requires that each and every element of the claimed invention be disclosed in the prior art. . . . [i]n addition, the prior art reference must be enabling, thus placing the allegedly disclosed matter in the possession of the public." *Akzo N.V. v. U.S. International Trade Commission*, 1 USPQ 2d 1241, 1245 (Fed. Cir. 1986), *cert. denied*, 482 U.S. 909 (1987). Furthermore, "[t]he Examiner bears the burden of presenting at least a *prima facie* case of anticipation." *In re Sun*, 31 USPQ 2d 1451, 1453. The Applicants submit the Examiner has failed to make a *prima facie* case of anticipation. That is to say, none of the art cited by the Examiner in the instant Action discloses each and every element of the invention as claimed.

While the Examiner alleges that numerous references disclose the administration of sterile leukotriene solutions, the Examiner presents no evidence to show that these references anticipate the Applicants' presently amended claims. That is to say in order to further their business interests and without acquiescing to the Examiner's arguments, while expressly reserving the right to prosecute claims as originally filed (or claims similar thereto), the Applicants have amended each of the pending independent claims such that the claimed solution comprises a *sterile liquid vehicle, an antibiotic* and a leukotriene dissolved in said sterile liquid vehicle, wherein said solution is *an aerosol*.

Specifically, the Applicants have further clarified their preferred embodiment, set out in each independent claim, by reciting antibiotics as discussed in the specification (see *Applicants' Specification* pg 6 ln 5-6). The Applicants submit that none of the cited references offered by the Examiner discloses or suggests a solution for the treatment of a microbial infection wherein said solution comprises a *sterile liquid vehicle, an antibiotic* and a leukotriene dissolved in said sterile liquid vehicle.¹ Furthermore, the art is also silent on the embodiments of the invention as claimed wherein said solution is in an intratracheal instillation device, said instillation device being selected from the group consisting of an endotracheal tube and a bronchoscope. The Applicants, therefore, respectfully request the Examiner withdraw all pending anticipation rejections.

B. The Claims Are Not Obvious' Under 35 U.S.C. § 103(a)

1. The Examiner Fails to Make A *Prima Facie* Case of Obviousness

The Examiner rejects, under 35 U.S.C. § 103(a), claims 22-25, and 27-37 as being unpatentable over Gosselin et al. (U.S. Patent 5,789,441; priority to February 15, 1996) in

¹ With regard to U.S. patent 5,789,441 to Gosselin et al., filed on February 11, 1997, Applicants note this patent (i.e. the '441 patent) is a Continuation-in-part of application serial number 08/602,059 filed February 15, 1996. Upon review of the specification in application serial number 08/602,059 (an uncertified copy of which is attached for the Examiner's reference at Tab 1), Applicants note Gosselin et al. are silent on the preparation of any therapeutic agent as an aerosol or a sterile solution. That is to say, Gosselin et al. only teach "aerosols" (Col. 11, line 31) and "sterile solutions" (Col. 12, line 15) in the Continuation-in-part application (e.g. the '441 patent) which *post dates* the priority date (i.e. December 03, 1996) of the Applicants' instant application. Therefore the '441 patent is not prior art, *vis-a-vis* the Applicants' claimed embodiments reciting an "aerosol" and a "sterile solution", as these limitations were first presented, by Gosselin et al., in an application the filing of which *post dates* the filing of the instant application. The '441 patent to Gosselin et al., therefore, cannot anticipate the embodiments of the invention as presently claimed.

view of Fujimura et al. (1991; Prostaglandins 42(4):379-389). The Examiner also rejects, under 35 U.S.C. § 103(a), claims 22-25, and 27-37 as being unpatentable over Gosselin et al. (U.S. Patent 5,789,441; priority to February 15, 1996) in view of Ludwig et al. (1998; J. Appl. Physiol. 65(3): 1424-1429). The Applicants respectfully disagree.

The Examiner is reminded a *prima facie* case of obviousness requires citation to a combination of references which (a) disclose the elements of the claimed invention, (b) suggests or motivates one of skill in the art to combine those elements to yield the claimed combination, and (c) provides a reasonable expectation of success should the claimed combination be carried out. Failure to establish any one of the these three requirements precludes a finding of a *prima facie* case of obviousness, and, without more, entitle the Applicants to allowance of the claims in issue. See, e.g., *Northern Telecom Inc. v. Datapoint Corp.*, 15 USPQ2d 1321, 1323 (Fed. Cir. 1990).

The Applicants respectfully submit the Examiner has failed to establish any of the three elements of a *prima facie* case of obviousness. In addressing this rejection, Applicants focus on independent claims 22, 28, and 33 since non-obviousness of an independent claim necessarily leads to non-obviousness of claims dependent therefrom. See, MPEP 2143.03.

2. The Cited Art Is Deficient

In the Office Action mailed July 15, 2003 the Examiner states that, "[t]he rejection of claims 22-25 and 27-37 under 35 U.S.C. 103(a) as being unpatentable over Gosselin et al. (USP 5,789,441; priority 15, 1996) as set for in the previous Office Action is withdrawn." Applicants respectfully submit the Examiner's subsequent combination of Gosselin with Fujimura et al. and Ludwig et al., in the pending Office Action, fails to remedy the deficiencies of Gosselin in view of the pending claim set.

3. No Motivation to Combine the References

A proper analysis, in view of 35 U.S.C. §103, demands the references cited by the Examiner be considered as whole and must suggest the desirability and, thereby, the obviousness of making the combination. *Hodash v. Block Drug Co., Inc.*, 786 F.2d 1136, 1143, n. 5, 229 USPQ 182, 187, n.5 (Fed. Cir. 1986). Applicants submit that references cannot be considered collectively until the Examiner points to some motivation to combine

said references. This analysis prevents the Examiner from using the instant Specification to reconstruct, in hindsight, the invention as claimed. The Federal Circuit, in a recent decision, articulated the policy behind this analysis:

To prevent the use of hindsight based on the invention to defeat patentability of the invention, this court requires the examiner to show a motivation to combine the references that create the case of obviousness. In other words, the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed.

See In re Rouffet et al., 149 F.3d 1350, 47 USPQ2d 1453 (Fed. Cir. 1998).

None of the prior art cited by the Examiner suggests the desirability of making the combination of elements which recapitulates the invention as claimed. In the Office Action mailed on July 15, 2003, the Examiner presents bald conclusions in place of reasoned motivation, as articulated by the Federal circuit, to combine the cited art. That is to say, the Examiner consistently invokes the mantra, "it would have been obvious. . ." to justify the modification of the cited art to provide missing elements of the invention as claimed.² The *Rouffet* court, however, admonishes against such an unsupported statements. Indeed, the Federal Circuit stated:

The Board did not . . . explain what specific understanding or technological principal within the knowledge of one of ordinary skill in the art would have suggested the combination. Instead, the Board merely invoked the high level of skill in the art. If such a rote invocation could suffice to supply a motivation to combine, the more sophisticated scientific fields would rarely, if ever, experience a patentable technological advance. Instead, in complex scientific fields, the Board could routinely identify the prior art elements in an application, invoke the lofty level of skill, and rest its case for rejection. To counter this potential weakness in the obviousness construct, the suggestion to combine requirement stands as a critical safeguard against hindsight analysis and rote application of the legal test for obviousness. *Rouffet*, 47 USPQ2d at 1458.

Indeed, the cited art provides *no motivation* to combine the references to teach the embodiment of the invention as presently claimed. Moreover, even if these references are *improperly* combined they do not recapitulate each and every element of the claimed embodiments of the present invention. Specifically, these references are silent on a solution

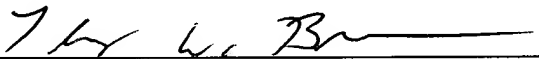
² See, pages six and seven of the Office Action mailed July 15, 2003.

comprising a solution, for the treatment of a microbial infection, comprising a *sterile liquid vehicle, an antibiotic* and a leukotriene dissolved in said sterile liquid vehicle wherein said solution is *an aerosol*. (emphasis added). Applicants respectfully submit, therefore, that the references cited are inadequate to sustain a rejection under 35 U.S.C. § 103(a).

CONCLUSION

The Applicants believe that the arguments and claim amendments set forth above traverse the Examiner's rejections and, therefore, request that all grounds for rejection be withdrawn, for the reasons set above, and that the instant application be passed to allowance. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, the Applicants encourage the Examiner to call the undersigned collect at 617.984.0616.

Dated: January 15, 2004



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UTILITY SERIAL NUMBER	PATENT NUMBER
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JEAN GOSSELIN, CAP-ROUGE, CANADA; PIERRE BORGEAT, SILLERY, CANADA: CHANG

CONTINUING DATA***
VERIFIED

FOREIGN/PCT APPLICATIONS***
VERIFIED

Foreign priority claimed 35 USC 119 conditions met	<input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> yes <input type="checkbox"/> no	AS FILED →	STATE OR COUNTRY CAX	SHEETS DRWGS. 10	TOTAL CLAIMS 20	INDEP. CLAIMS	FILING FEE RECEIVED	ATTORNEY'S POCKET NO.
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LEUKOTRIENE B4 AS AN ANTIVIRAL AGENT

U.S. DEPT. OF COMMERCE PAT. & TM. CPTO-436L (Rev. 12-84)

PATENT OF APPLICATION FILED SEPARATELY	
NUMBER OF ALLOWANCE MAILED	
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PATENT APPLICATION



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ABANDONED

1. Application papers

2. *Rejection on 3/11/99*

3. *Office of Appeal*

4. *Request for Extension of Time*

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SERIAL NUMBER <div style="text-align: center; margin-top: 10px;">08/602,059</div>	FILING DATE <div style="text-align: center; margin-top: 10px;">02/15/96</div>	CLASS. <div style="text-align: center; margin-top: 10px;">424</div>	GROUP ART UNIT <div style="text-align: center; margin-top: 10px;">1806</div>		
APPLICANT	JEAN GOSSELIN, CAP-ROUGE, CANADA; PIERRE BORGEAT, SILLERY, CANADA. **CONTINUING DATA***** VERIFIED <div style="border-bottom: 1px solid black; width: 100px; margin-top: 10px;"></div> **FOREIGN/PCT APPLICATIONS***** VERIFIED <div style="border-bottom: 1px solid black; width: 100px; margin-top: 10px;"></div>				
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TITLE	LEUKOTRIENE B4 AS AN ANTIVIRAL AGENT				
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PATENT APPLICATION SERIAL NO. 08/602059

U.S. DEPARTMENT OF COMMERCE
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LEUKOTRIENE B₄ AS AN ANTIVIRAL AGENT

BACKGROUND OF THE INVENTION

(a) Field of the Invention

5 The invention relates to the demonstration of the antiviral activity of leukotriene B₄ (LTB₄) which might serve as a therapeutic agent in viral infections caused by human and animal viruses.

(b) Description of Prior Art

10 Many important infectious diseases afflicting mankind are caused by viruses. Some are important because they are frequently fatal; among such are rabies, smallpox, poliomyelitis, hepatitis, yellow
15 fever, immune deficiencies and various encephalitic diseases. Others are also important because they are very contagious and create acute discomfort such as
20 influenza, measles, mumps and chickenpox, as well as respiratory-gastrointestinal disorders. Others such as rubella and cytomegalovirus can cause congenital
25 abnormalities. Finally, there are viruses, known as oncoviruses, that can cause tumors and cancer in humans and animals.

 Among viruses, the family of Herpesviridae is of great interest. Herpesviruses are highly disseminated in nature and highly pathogenic for man. For
25 example, Epstein-Barr virus (EBV) is known to cause infectious mononucleosis in late childhood, adolescence or in young adults. The hallmarks of acute infectious mononucleosis are sore throat, fever, head-
30 ache, lymphadenopathy, enlarged tonsils and atypical dividing lymphocytes in the peripheral blood. Other manifestations frequently include mild hepatitis, splenomegaly and cerebritis (for review see Miller G.,
In: Virology, B.N. Fields & D.M. Knipe ed., Raven Press, 1990, pp. 1921-1958). EBV is also associated to
35 two forms of cancer: Burkitt's lymphoma (BL) and the

nasopharyngeal carcinoma (NPC). In endemic areas of equatorial Africa, BL is the most common childhood malignancy, accounting for approximately 80% of cancers in children. While moderately observed in North American Caucasians, NPC is one of the most common cancers in Southern China with age incidence of 26 to 55. EBV, like the cytomegalovirus, is also associated to the post-transplant lymphoproliferative disease, which is a potentially fatal complication of chronic immunosuppression following solid organ or bone marrow transplantation.

Another Herpesvirus, named Herpes Simplex type 1 (HSV-1) is identified as the etiologic agent of gingivostomatitis. Manifestations are fever, sore throat, ulcerative and vesicular lesions in the mouth. The most severe clinical state caused by HSV is the primary genital herpetic infection. While HSV-1 can cause genital herpetic infection, HSV-2 is the main virus associated to this disease. This HSV infection is accompanied by vesicles, pustules and ulcers causing lesions on genital parts. A urinary retention syndrome may also be encountered. More than 80% of people are seropositive to HSV-1 or HSV-2 and studies have indicated a frequency of recurrence or viral reactivation as high as 60%. Other diseases are also associated to HSV such as skin and eye infections such as chorioretinitis or kerato-conjunctivitis. Approximately 300,000 cases of HSV infections of the eye are diagnosed yearly in United States.

Human Herpes virus-6 (HHV-6) has a marked tropism for cells of the immune system and therefore, HHV-6 infection may result in alteration of the immune response. It is now clear that HHV-6 is the cause of exanthem subitum as a primary infection in children. Recent studies indicate that a significant proportion of organ transplant recipients which are seropositive

before transplantation, demonstrate serologic evidence of reactivation subsequent to immunosuppression. Heterophil-negative mononucleosis-like illness and non-A, non-B hepatitis also have been associated to active
5 HHV-6 infection. HHV-6 has often been isolated from patients with human immunodeficiency virus (HIV) infections. The fact that HIV and HHV-6 can reside in the same target cell have led to the speculation that HHV-6 infection may act as a cofactor in the progression of HIV-seropositive patients to symptomatic AIDS.
10 Recent studies also suggest that a human herpesvirus is closely associated to HIV diseases. In fact, Kaposi sarcoma (KS), a neoplasm occurring mainly in HIV-infected person, was found to have an infectious etiology. While the virus has been named KS-associated herpesvirus, its formal classification is likely
15 to be HHV-8.

In all infectious diseases, the efficacy of therapy often depends on the host immune response.
20 This is particularly true for Herpesviruses; indeed, the ability of all Herpesviruses to establish latent infections results in an extremely high incidence of reactivated infection in immunocompromised patients. In renal transplant recipients, 40% to 70% reactivate
25 latent HSV infections, and 80% to 100% reactivate CMV infections. Such viral reactivations have also been observed in HIV-positive patients (AIDS).

Today, the number of therapeutic agents used for the treatment of viral infections remain relatively limited. For example, four major compounds are
30 mainly used in the treatment of Herpesvirus infections: Idoxuridine, Vidarabine, Acyclovir and Ganciclovir. Their efficacy is limited and they cause many side effects. Allergic effects have been reported in
35 35% of patients treated with Idoxuridine which is used only to treat HSV infection of the eye. The most com-

mon side effects of Vidarabine are gastrointestinal disturbances (15% of patients). The major side effect of Acyclovir is the alteration of renal function. Since Acyclovir is a nucleoside analog that can be incorporated in both viral and host cell DNA, normal division of host cell can be affected. Regarding Ganciclovir, the most important side effects are neutropenia and thrombocytopenia that occur in about 40% of AIDS patients.

10 Thus, there is an urgent need for the development of more efficacious therapeutic agents for the treatment of viral infections with fewer side effects.

Leukotriene B₄ (LTB₄ [5S,12R-6,8,10,14(Z,E,E,Z)-eicosatetraenoic acid]) is a known
15 natural molecule with many reported biological properties. In fact, LTB₄ is a metabolite of arachidonic acid which is derived from the 5-lipoxygenase pathway. LTB₄ is considered as a potent pro-inflammatory compound; its most important biological activity is its
20 chemotactic and chemokinetic effects on leukocytes. Indeed, LTB₄ has been shown to be a potent chemoattractant for human polymorphonuclear leukocytes, monocytes and macrophages, both *in vitro* and *in vivo*. LTB₄ also activates other leukocyte functions such as
25 degranulation and superoxide anion synthesis. Because of these pro-inflammatory effects, LTB₄ is considered as a putative component in defense mechanisms. Moreover, LTB₄ is synthesized by inflammatory cells such as polymorphonuclear leukocytes, monocytes and macro-
30 phages.

LTB₄ has also been shown to exert immunomodulatory activities. Indeed, LTB₄ was found to induce suppressor cell activity in human peripheral blood mononuclear leukocyte cultures; the induced suppressor
35 cell activity inhibited the proliferative response of human lymphocytes to mitogens (Rola-Pleszczynski M.,

et al., *BioChem. Biophys. Res. Comm.*, 1982, 108:1531).
It was also shown that LTB₄ increases human natural
cytotoxic cell activity against K562 erythroleukemia
cells and against the human prostatic adenoma MA-160
5 cells either uninfected or persistently infected with
Herpes simplex virus type 1 (HSV-1) (Rola-Pleszczynski
M., et al., *BioChem. Biophys. Res. Comm.*, 1983,
113:531; Gagnon L., et al., *Cell Immunol.*, 1987,
110:243). Other studies indicated that in addition to
10 LTB₄, LTA₄, LTD₄, 5-hydroperoxy-eicosatetraenoic acid
and 15-hydroperoxy-eicosatetraenoic acid also enhanced
human natural killer cell cytotoxicity
(Rola-Pleszczynski, M., et al, *Prostaglandins Leu-
kotrienes Med.*, 1984, 13:113; Rossi P., et al., *Cell*
15 *Immunol.*, 1985, 93:1).

To date, there is no report of antiviral activ-
ity of LTB₄.

A family of molecules collectively called the
prostaglandins (prostaglandins A, B, D, J, E and I)
20 which are structurally related to LTB₄, have been
repeatedly demonstrated to exert antiviral and
anti-cancer activity both in in vitro and in vivo sys-
tems. The prostaglandins are also derived from
arachidonic acid but originate from a different bio-
25 synthetic pathway, the cyclooxygenase pathway.

United States Patent No. 4,689,426 issued on
August 25, 1987 in the names of Sugiura et al.
describes cyclopentenone derivatives related to pro-
staglandin A or D which possess anti-tumor and antivi-
30 ral activities.

Although, the prostaglandins may have been
shown to have some antiviral activities, they all
caused undesirable side effects and appear to be much
less active, on a molar basis, than LTB₄ when tested
35 in vitro.

It would be highly desirable to be provided with an antiviral agent with greater efficacy and which would not present the undesirable side effects of the known antiviral agents.

5

SUMMARY OF THE INVENTION

The expression "human and animal viruses" is intended to include, without limitation, DNA and RNA viruses in general and Retroviridae. DNA viruses include parvoviridae, papovaviridae, adenoviridae, herpesviridae, poxviridae and hepadnaviridae. RNA viruses include picornaviridae, togaviridae, orthomyxoviridae, paramyxoviridae, coronaviridae, reoviridae, oncornaviridae and filoviridae.

15 One aim of the present invention is to provide an antiviral agent which would be more efficacious for the prophylaxis and treatment of viral infections and would not present the undesirable side effects of the known antiviral agents.

20 Another aim of the present invention is to provide an antiviral agent for the prophylaxis or treatment of cancers induced by oncoviruses such as retroviruses, papillomaviruses, adenoviruses and herpesviruses.

25 Another aim of the present invention is to provide an antiviral agent for the prophylaxis or treatment of viral infections in immunosuppressed patients and animals.

30 Another aim of the present invention is to provide an anticancer agent for the treatment of cancer.

Another aim of the present invention is to provide a therapeutic agent for the treatment of bacterial and fungal infections.

35 In accordance with the present invention there is provided the use of leukotriene B₄ (LTB₄) agent as an antiviral agent against Herpesviruses selected from

the group consisting of EBV, HSV-1, HSV-2, CMV, VZV, HHV-6, HHV-7, HHV-8.

5 In accordance with the present invention there is provided the use of LTB₄ agent as antiviral agent against HIV-1 and HIV-2 and against other human and animal viruses, including, but not limited to, porcine enteroviruses belonging to the picornaviridae or bovine diarrhea virus belonging to the Togaviridae family, or bovine respiratory syncytial virus belong-
10 ing to the paramyxoviridae.

In accordance with the present invention there is provided the use of LTB₄ agent as an antiviral agent in the treatment of viral infections in humans and animals in association with other antiviral
15 agents, including but not limited to interferon- α , - β , - γ , tumor necrosis factor α , Ganciclovir, Acyclovir, Vidarabine, Idoxuridine, and prostaglandins or prostaglandin analogs.

In accordance with the present invention, there
20 is provided the use of LTB₄ agent as an antiviral agent for the prophylaxis and treatment of cancers induced by oncoviruses such as retroviruses, papillomaviruses, adenoviruses and herpesviruses.

In accordance with the present invention, there
25 is provided the use of LTB₄ agent as an antiviral agent against cancers induced by oncoviruses in association with other anticancer agents including but not limited to adriamycine, cyclophosphamide and methotrexate.

30 In accordance with the present invention, there is provided the use of LTB₄ agent as an antiviral agent for the prophylaxis and treatment of viral infections in immunosuppressed patients and animals.

Immunosuppressed patients include patients who
35 underwent organ or tissue transplantation and are treated with immunosuppressive agents including but

not limited to azathioprine, corticosteroids, adriamycine, cyclophosphamide and methotrexate. Immunosuppressed patients also include patients with any form of cancer or neoplastic diseases treated or
5 not with anticancer chemotherapeutic agents including but not limited to adriamycine, cyclophosphamide and methotrexate. Immunosuppressed patients also include patients with inflammatory diseases treated with anti inflammatory agents including but not limited to
10 corticosteroids, methotrexate, azathioprine and cyclophosphamide. Immunosuppressed patients also include patients with shock or severe trauma including but not limited to burn injury, or patients undergoing chronic hemodialysis.

15 In accordance with the present invention, there is provided the use of LTB₄ agent as an antiviral agent against viral infections in immunosuppressed patients and animals in association with other antiviral agents.

20 In accordance with the present invention, there is provided the use of LTB₄ agent as an anticancer agent for the treatment of cancers.

In accordance with the present invention, there is provided the use of LTB₄ agent as an anticancer
25 agent for the treatment of cancers in association with other anticancer agents including but not limited to adriamycine, cyclophosphamide and methotrexate.

In accordance with the present invention, there is provide the use of LTB₄ agent as a therapeutic
30 agent against bacterial Gram + and - infections or fungal infections, alone or in association with other antibacterial or antifungal agents.

BRIEF DESCRIPTION OF THE DRAWINGS

35 Fig. 1 illustrates the effects of LTB₄ on clump formation induced by EBV;

Fig. 2 illustrates the effects of LTB₄ on EBV-induced synthesis of EBNA protein;

Fig. 3 shows the inhibition of the HSV-1 induced cytopathic effect (formation of syncicia) by
5 LTB₄;

Fig. 4 shows the effect of LTB₄ on cell viability; and

Fig. 5 illustrates a comparative study (one experiment) of the effects of LTB₄ and Acyclovir on
10 clump formation induced by EBV (A) and also on EBV-induced synthesis of EBNA protein (B).

DETAILED DESCRIPTION OF THE INVENTION

The leukotriene B₄ (LTB₄) agent of the present
15 invention is either LTB₄ or certain related compounds, all of which are polyunsaturated fatty acids. They are either natural substances produced by activated mammalian blood cells or analogs of such natural substances. All of the LTB₄ agents can be obtained by
20 chemical synthesis by methods described in the literature and most are commercially available.

As used herein, the term "LTB₄ agent" means one or more of the following polyunsaturated fatty acids, which in addition to LTB₄ itself, are analogs of LTB₄,
25 or precursors or metabolites of LTB₄ or LTB₄ analogs: LTB₄, 14,15-dihydro-LTB₄, 17,18-dehydro-LTB₄, 19-hydroxy-LTB₄, 20-hydroxy-LTB₄ and their 5(R)-hydroxy, 5-keto, 5(S)-hydroperoxy, 5(R)-hydroperoxy and 5-deoxy analogs; LTA₄; 17,18-dehydro-LTA₄; 5(S)-hydroxy-
30 6,8,11,14(E,Z,Z,Z)-eicosatetraenoic acid ("5-HETE"), 14,15-dihydro-5-HETE, 17,18-dehydro-5-HETE, and their 5(R)-hydroxy, 5-keto, 5(S)-hydroperoxy, 5(R)-hydroperoxy analogs; 12(R)-hydroxy-5,8,10,14(Z,Z,E,Z)-eicosatetraenoic acid ("12-HETE"), 14,15-dihydro-12-
35 HETE, 17,18-dehydro-12-HETE and their 12-keto and 12-

hydroperoxy analogs; and 12-oxo-5,8,10(Z,Z,E)-dodecatrienoic acid.

The term LTB₄ agent also includes variants where a modification is introduced into the molecule by reacting targeted functional groups of the fatty acid with an organic derivatizing agent that is capable of reacting with the selected functional group or to cause intramolecular rearrangement (such as the formation of lactones with hydroxylated fatty acids). The resulting compounds may have altered biological activity and/or bioavailability. Thus, the covalently modified fatty acid can be a pro-drug with reduced biological activity which upon in vivo administration is slowly transformed into a more active molecule (underivatized LTB₄ agent). Variants may also be metabolically stable and biologically active analogs of LTB₄ agents altered in a way that will result in retarded disposition of the compound (decreased metabolism and/or elimination). Variants with modifications at the omega end (for instance, 20,20,20-trifluoromethyl-LTB₄) show increased resistance to omega-oxidation (a catabolic process of unsaturated fatty acids) and variants with modifications at the carboxylic end, at the level of carbon 1, 2 or 3 (for example, 3-thio-LTB₄, 3-hydroxy-LTB₄, LTB₄ methylsulfonylamide, LTB₄ methylamide, 1-tetrazide LTB₄), show increased metabolic resistance to beta-oxidation and/or to elimination (such as uptake by probenecid-sensitive organic acid transporter). Other variants are analogs of LTB₄ agents with minimal structural changes, such as increased or decreased chain length (chain length of 17 or 18 or 19 or 21 or 22 or 23 carbons instead of 20), additional double bond(s), deleted double bond(s), altered double bond geometry (cis to trans or vice versa), or where the positions of one or two functional groups and/or one

or more of the double bonds have been moved one or two carbons relative to the omega end. The LTB₄ agent may be a variant carrying one or several of the above mentioned structural modifications. The LTB₄ agents and
5 variants of LTB₄ agents show significant biological activity analogous to that of LTB₄ in various biological systems, including but not limited to the activation of human neutrophils, and are thus likely to exert an antiviral activity similar to that of LTB₄.
10 They are included within the scope of this invention. The term LTB₄ agent also includes antibodies to the LTB₄ receptor, or anti-idiotypic antibodies to antibodies raised against LTB₄ or one of the above-mentioned analogs or variants of LTB₄, which might elicit
15 an LTB₄-like biological response, such as an antiviral effect.

The antiviral activity of LTB₄ against two Herpesviruses, EBV and HSV-1 have been studied. Human peripheral blood mononuclear cells were cultured in
20 the presence or absence of LTB₄ at three different concentrations. After twelve days of culture (single addition of LTB₄ on day 1), two parameters were evaluated: the formation of clumps or rosettes, which morphologically characterizes the EBV-infected cells, and
25 the presence of Epstein-Barr Virus Nuclear Antigen (EBNA), a viral antigen synthesized in EBV-infected cells. The results obtained show that LTB₄ markedly affected the formation of clumps. Similarly, the percentage of EBNA-positive cells was strongly decreased
30 by more than 80% with 0.3 nM LTB₄ and almost totally with a concentration of 3 nM. The cytotoxic effect of HSV-1 infection was monitored by the presence of large multinucleated cells (syncytia). Again, the presence
35 of LTB₄ in the cell culture media strongly decreased the formation of syncytia induced by HSV-1. Interestingly, in all cellular cultures, the cell viability

was comparable to that of the unstimulated cells (controls) cultured during the same period of time, indicating that LTB₄ exerts no direct cytotoxic effect on the cells. Furthermore, in one experiment, LTB₄ was
5 found to inhibit (> 50%) the viral replication of EBV using the B95-8 cell lines. These results clearly show that LTB₄ exerts a very potent antiviral effect against two Herpesviruses without cytotoxic effect on the uninfected cells. It is noteworthy that Ganciclovir was shown to have IC₅₀ values of 1 and 2.4 μM
10 in in vitro assays of viral replication (EBV and HSV, respectively) (Matthews and Boehms, *Rev Inf. Dis.*, 1988, 10, suppl. 3:490). Preliminary comparative study shows that LTB₄ exerts potent antiviral activities as
15 compared to Acyclovir. It is possible that the structure of LTB₄ could be modified in order to provide a molecule with even higher antiviral activity or alternatively, a molecule with increased bioavailability (for example, decreased lipophilicity or enhanced
20 resistance to metabolism in vivo).

Thus, the results suggest that LTB₄ can be useful in the treatment of viral infections in humans and animals. Because the data show that LTB₄ exerts antiviral activity against 2 types of viruses, and
25 thus is not specific to a single type of virus, it might be useful for the treatment of viral infections caused by any type of viruses.

The present invention will be more readily understood by referring to the following examples which
30 are given to illustrate the invention rather than to limit its scope.

EXAMPLE I

Assay for EBV-induced clump formation and EBNA synthesis in peripheral blood mononuclear cells

Clump formation

5 Peripheral blood mononuclear cells (PBMC) were obtained from healthy donors after dextran sedimentation and centrifugation on Ficoll-Paque™ gradients as previously described by Boyum A. (*Scand. J. Immunol.*, 1976, 5(5):9). Cells were resuspended in RPMI-1640
10 medium supplemented with 10% heat inactivated FCS in the presence of infectious EBV, strain B95-8, at a viral titer of 10^7 transforming units (TFU)/ml. When indicated, EBV-infected PBMC were simultaneously treated with different concentrations of LTB₄, i.e.
15 0.3, 3.0 and 30 nM, respectively. Cells were cultured in 96-well microplates (10^6 cells/ml at 200 µl/well) during twelve days, and clump formation, which characterizes the EBV-infected cells was evaluated with an inverted microscope (100 X) (Figs. 1A, 1B, 1C).

20 Cells were cultured in microplates and the clumps were counted in each well. Results show the mean number of clumps per well + S.D. in 3 different experiments (A,B,C) (A, n = 24 wells; B, n = 36 wells; C, n = 36 wells). NS: nonstimulated cells.

25 Detection of EBNA antigen

 After twelve days of culture, cells were harvested for determination of the presence of EBNA antigen, a consequence of EBV infection. Preparation of cell smears, fixation and detection of EBNA by the
30 anti-complement immunofluorescence (ACIF) test were carried out as described by Reedman B.M. and Klein G. (*Int. J. Cancer*, 1973, 11:499). Smears were prepared by spreading 50 µl of a concentrated suspension of washed cells (2×10^6 /ml) on clean slides, air dried
35 and fixed in cold acetone (-20°C) during 10 minutes.

Human serum (50 μ l) from EBV seropositive donor was used as a source of complement. Slides were incubated at room temperature in a humid chamber during 45 minutes. Slides were then washed three times in phosphate buffer saline (PBS) and stained with 50 μ l of fluorescein-5-isothiocyanate (FITC "Isomer I")-conjugated goat IgG fraction anti-human complement C3 (Cappel) during 60 minutes at room temperature in a humid chamber. Slides were washed in PBS (3 times) and mounted in PBS:glycerol 1:1 and examined. Raji and U937 cells were used as positive and negative controls, respectively (Figs. 2A, 2B & 2C).

Detection of EBNA was evaluated by the anti-complement immunofluorescence (ACIF) test. Data show the means of 24, 36 and 36 cultures for donor A, B and C, respectively. Cells not exposed to EBV showed no detectable EBNA antigen.

EXAMPLE II

20 Assay for HSV-1 infection

PBMC were infected with HSV-1 (strain McIntyre) at a TCID₅₀ of 10^7 /ml, and treated or not with different concentrations of LTB₄ (0.3, 3.0 and 30 nM) as described in Example I. Infection of PBMC was monitored by the formation of large multinucleated cells (syncytia) (Fig. 3).

Results are representative of 8 cultures from two different donors and are given in arbitrary units: positive, 8 to 10; moderately positive, 4 to 7; weakly positive, 1 to 3. Cells not exposed to HSV-1 do not form syncytia.

EXAMPLE III

Assay for LTB₄ cytotoxicity

In cell cultures described in Examples I and II, the cytotoxic effect of LTB₄ was assessed by the trypan blue dye exclusion test at concentrations up to 30 nM. LTB₄ was found to exert no cytotoxic effect

(Fig. 4). Cell viability was assessed by the trypan blue exclusion test; values (from 1 experiment representative of 3) represent the mean cell viability in cell cultures (n = 24).

EXAMPLE IV

Comparative antiviral effects of LTB₄ and acyclovir on EBV infection

PBMC (10⁶ cells/ml) were cultured in microplates (96 wells) at 2 x 10⁵ cells/well and infected with EBV (10⁷ TFU/ml) as described in Example I. At one hour post-infection, cell cultures were treated with LTB₄ (3 nM) or with different concentrations of Acyclovir (acycloguanosine), i.e. 1000 or 3000 nM. After seven days of incubation, clump formation (Fig. 5A) and EBNA synthesis (Fig. 5B) were evaluated as described in Example I.

Clump formation was evaluated in microplates and detection of EBNA was performed by the ACIF test on 36 cultures.

While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure as come within known or customary practice within the art to which the invention pertains and as may be applied to the essential features hereinbefore set forth, and as follows in the scope of the appended claims.

WE CLAIM:

1. The use of leukotriene B₄ (LTB₄) agent as an antiviral agent against human and animal viruses.
2. The use of claim 1, wherein said human and animal viruses are selected from the group consisting of DNA viruses, RNA viruses and Retroviridae.
3. The use of claim 2, wherein said DNA viruses are selected from the group consisting of parvoviridae, papovaviridae, adenoviridae, herpesviridae, poxviridae and hepadnaviridae.
4. The use of claim 3, wherein said herpesviridae is selected from the group consisting of EBV, HSV-1, HSV-2, CMV, VZV, HHV-6, HHV-7, HHV-8.
5. The use of claim 2, wherein said RNA viruses are selected from the group consisting of picornaviridae, togaviridae, orthomyxoviridae, paramyxoviridae, coronaviridae, reoviridae, oncornaviridae and filoviridae.
6. The use of claim 5, wherein said togaviridae virus is a bovine diarrhea virus.
7. The use of claim 5, wherein said picornaviridae virus is a porcine enterovirus.
8. The use of claim 5, wherein said animal virus is a paramyxoviridae or bovine respiratory syncytial virus.

9. The use of claim 2, wherein said human virus is a Retroviridae selected from HIV-1 and HIV-2.

~~10~~. The use of LTB₄ agent as an antiviral agent in the prophylaxis and treatment of viral infections in humans and animals in association with different antiviral agents.

11. The use of claim 10, wherein said different antiviral agents are selected from the group consisting of interferon- α , - β , - γ , tumor necrosis factor α , Ganciclovir, Acyclovir, Vidarabine, Idoxuridine, prostaglandins and prostaglandin analogs.

~~12~~. The use of LTB₄ agent as an antiviral agent in the prophylaxis and treatment of cancer induced by oncogene viruses.

~~13~~. The use of LTB₄ agent as an antibacterial agent against Gram positive and negative microorganisms.

~~14~~. The use of LTB₄ agent as an antiviral agent for the prophylaxis or treatment of viral infections in immunosuppressed patients and animals, or in patients treated with drugs known to enhance the occurrence of viral infections.

15. The use of claim 14, wherein said drugs are selected from the group consisting of azathioprine, corticosteroids, adriamycine, cyclophosphamide and methotrexate.

~~16~~. The use of LTB₄ agent as an anticancer agent for the treatment of cancers.

17. The use of LTB₄ agent as an anticancer agent for the treatment of cancers in association with other anticancer agents selected from the group consisting of adriamycine, cyclophosphamide and methotrexate.

18. The use of LTB₄ agent as an antibacterial agent in the treatment of bacterial infections in humans and animals in association with other antibacterial agents.

19. The use of LTB₄ agent as an antifungal agent against fungal infections in humans and animals in association or not with other antifungal agents.

20. The use according to any of claims 1 to 19, wherein said LTB₄ agent is selected from the group consisting of:

LTB₄; 14,15-dihydro-LTB₄; 17,18-dehydro-LTB₄,
19-hydroxy-LTB₄; 20-hydroxy-LTB₄ and
5(R)-hydroxy, 5-keto, 5(S)-hydroperoxy,
5(R)-hydroperoxy and 5-deoxy analogs thereof;
LTA₄; 17,18-dehydro-LTA₄; 5(S)-hydroxy-
6,8,11,14(E,Z,Z,Z)-eicosatetraenoic acid
("5-HETE"); 14,15-dihydro-5-HETE; 17,18-dehy-
dro-5-HETE; and 5(R)-hydroxy, 5-keto,
5(S)-hydroperoxy, 5(R)-hydroperoxy analogs
thereof;
12(R)-hydroxy-5,8,10,14(Z,Z,E,Z)-eicosatet-
raenoic acid ("12-HETE"); 14,15-dihydro-12-
HETE; 17,18-dehydro-12-HETE and 12-keto and 12-
hydroperoxy analogs thereof; and
12-oxo-5,8,10(Z,Z,E)-dodecatrienoic acid,
and variants thereof.



ABSTRACT OF THE INVENTION

The present invention relates to the use of the antiviral activity of leukotriene B₄ (LTB₄), variants and derivatives thereof as a therapeutic agent in viral infections caused by human and animal viruses. The present invention also relates to the use of LTB₄ as an anticancer agent in the prophylaxis and treatment of cancers induced by tumor viruses and in other neoplastic diseases. The human and animal viruses are DNA viruses, such as parvoviridae, papovaviridae, adenoviridae, herpesviridae, poxviridae and hepadnaviridae; RNA viruses, such as picornaviridae, togaviridae, orthomyxoviridae, paramyxoviridae, coronaviridae, reoviridae, oncornaviridae and filoviridae in general; and Retroviridae such as HIV-1 and HIV-2.

602059

Combined Declaration for Patent Application and Oath of Attorney

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe that I am the original, first and sole inventor (if only one name listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled LEUKOTRIENE B₄ AS AN ANTIVIRAL AGENT, the specification of which

☒ is attached hereto.

☐ was filed on _____ as Application No. _____

and (if applicable) was amended on _____

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, § 1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code § 119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having filing date before that of the application on which priority is claimed;

Prior Foreign Application(s)

Number	Country	Day/Month/Year Filed	Priority Claimed
_____	_____	_____	_____
_____	_____	_____	_____

I hereby claim the benefit under Title 35, United States Code, § 120 of any United States Application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States code, § 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, § 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

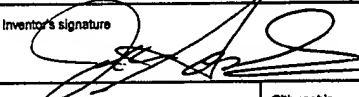
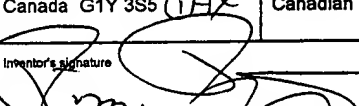
Application Serial No.	Day/Month/Year Filed	Status (Patented, Pending, Abandoned)
_____	_____	_____
_____	_____	_____

I hereby appoint the following attorneys, with full power of substitution, association, and revocation, to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith.

ROBERT MITCHELL, Registration No. 25,007; GUY HOULE, Registration No. 24,971; PAUL MARCOUX, Registration No. 24,890; KEVIN P. MURPHY, Registration No. 26,674; ROBERT CARRIER, Registration No. 30,728; MICHEL J. SOFIA; Registration No. 37,017; and FRANCE CÔTÉ, Registration No. 37,037; JAMES ANGLEHART, Reg. No. 38,796, and address all correspondence to:

SWABEY OGILVY RENAULT
1981 McGill College Ave., Suite 1600
Montreal, Quebec, Canada
H3A 2Y3
Telephone No. (514) 845-7128

I hereby further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of sole or first inventor <u>Jean Gosselin</u>	Inventor's signature 	Date <u>6/2/96</u>
Residence and Post Office address 1430 Esther-Blondin, #204, Cap-Rouge, Québec, Canada G1Y 3S5 <u>CAX</u>	Citizenship Canadian	
Full name of second inventor <u>Pierre Borgeat</u>	Inventor's signature 	Date <u>6/2/96</u>
Residence and Post Office address 2100 Brûlar, Sillery, Québec, Canada G1T 1G3 <u>CAX</u>	Citizenship Canadian	

602059

Applicant or Patentee: Jean Gosselin et al.
 Serial or Patent No.: _____ Atty. Dkt. No.: 12898-1"US" FC/d

Filed or Issued: _____
 For: LEUKOTRIENE B₄ AS AN ANTIVIRAL AGENT



VERIFIED STATEMENT (DECLARATION) CLAIMING SMALL ENTITY STATUS
[37 CFR 1.9(f) AND 1.27 (c)] - SMALL BUSINESS CONCERN

I hereby declare that I am

- ☒ (X) the owner of the small business concern identified below;
☐ () an official of the small business concern empowered to act on behalf of the concern identified below:

NAME OF CONCERN VIROCELL INC.
 ADDRESS OF CONCERN 2750 rue Einstein, Bureau 110
Sainte-Foy, Québec, Canada G1P 4R1

I hereby declare that the above identified small business concern qualifies as a small business concern as defined in 13 CFR 121.3-18, and reproduced in 37 CFR 1.9(d), for purposes of paying reduced fees under section 41(a) and (b) of Title 35, United States Code, in that the number of employees of the concern, including those of its affiliates, does not exceed 500 persons. For purposes of this statement, (1) the number of employees of the business concern is the average over the previous fiscal year of the concern of the persons employed on a full-time, part-time or temporary basis during each of the pay periods of the fiscal year, and (2) concerns are affiliates of each other when either, directly or indirectly, one concern controls or has the power to control the other, or a third party or parties controls or has the power to control both.

I hereby declare that rights under contract or law have been conveyed to and remain with the small business concern identified above with regard to the invention, entitled LEUKOTRIENE B₄ AS AN ANTIVIRAL AGENT by inventor(s) Jean Gosselin; and Pierre Borgeat described in:

- ☒ (X) the specification filed herewith;
☐ () application serial no. _____, filed _____;
☐ () patent no. _____, issued _____.

If the rights held by the above identified small business concern are not exclusive, each individual, concern or organization having rights to the invention is listed below* and no rights to the invention are held by any person, other than the inventor who could not qualify as an independent inventor under 37 CFR 1.9(c) if that person made the invention, or by any concern which would not qualify as a small business concern under 37 CFR 1.9(d) or a nonprofit organization under 37 CFR 1.9(e). *NOTE: Separate verified statements are required from each named person, concern or organization having rights to the invention averring to their status as small entities. [37 CFR 1.27]

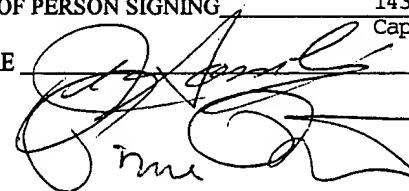
NAME _____
 ADDRESS _____
☐ () INDIVIDUAL ☐ () SMALL BUSINESS CONCERN ☐ () NONPROFIT ORGANIZATION

NAME _____
 ADDRESS _____
☐ () INDIVIDUAL ☐ () SMALL BUSINESS CONCERN ☐ () NONPROFIT ORGANIZATION

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. [37 CFR 1.28(b)]

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

NAME OF PERSON SIGNING	<u>Jean Gosselin</u>	<u>Pierre Borgeat</u>
TITLE OF PERSON OTHER THAN OWNER	<u>President</u>	<u>Vice President</u>
ADDRESS OF PERSON SIGNING	<u>1430 Esther-Blondin, #204</u>	<u>2100 Brûlart</u>
	<u>Cap-Rouge, QC, G1Y 3S5</u>	<u>Sillery, QC, G1T 1G3</u>

SIGNATURE  DATE 6/2/96

08/602059



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

File No. 12898-1"US" FC/ld

STANT COMMISSIONER FOR PATENTS,
Washington, D.C. 20231

Sir:

Transmitted herewith for filing is the patent application of

Inventor(s): Jean GOSSELIN et al.

For: LEUKOTRIENE B₄ AS AN ANTIVIRAL AGENT

Your petitioner prays that letters patent may be granted for the invention set forth in the enclosed specification including a disclosure, claims and declaration.

Enclosed are :

- ☒ 10 sheet(s) of drawings.
- ☒ An additional copy of this sheet and an Assignment of the Invention to VIROCELL INC.
- ☐ A certified copy of _____ on the basis of which the benefit of priority under 35 U.S.C. 119 is claimed.
- ☒ Declaration of small entity status.

	No. filed	Number Extra	Rate	Basic Fee \$375.00
Total Claims	20			
Multiple Dependency Fee	-	-		-
Independent Claims	9	6	\$39.00	234.00
			Base Filing Fee	375.00
			Assignment Fee	40.00
			Total	649.00

A cheque including the amount of \$649.00 to cover the Government Assignment, Filing and Extra Claims Fee is enclosed.

The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Account No. 19-5113.

Franc Côté

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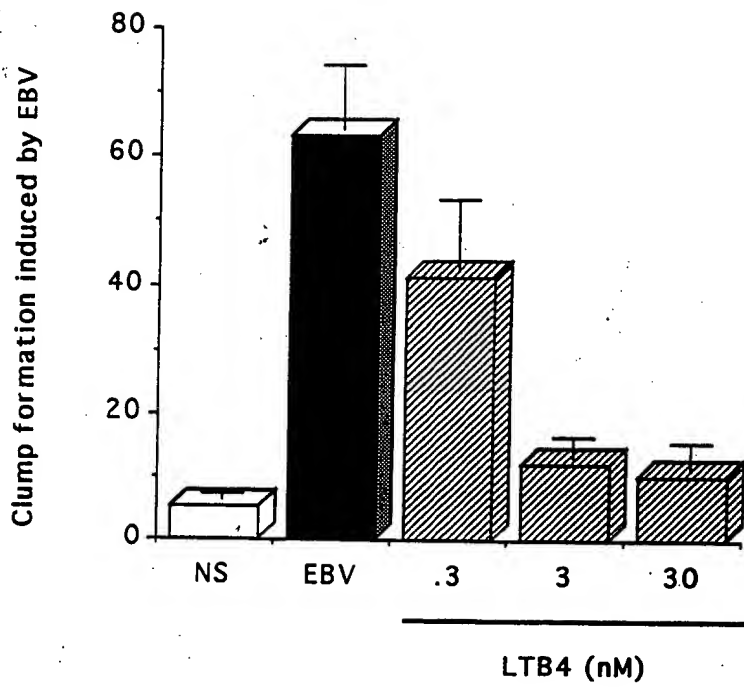


Fig. 1A

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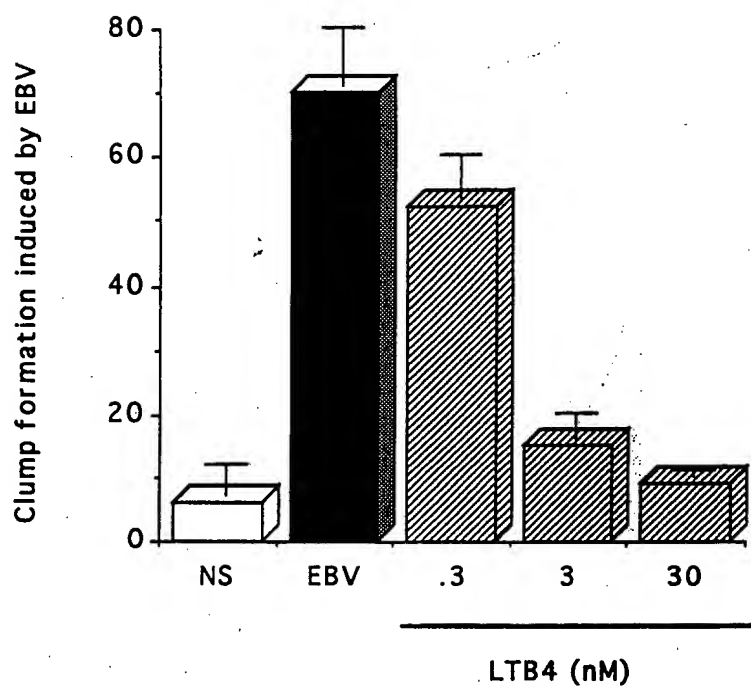


Fig. 1B

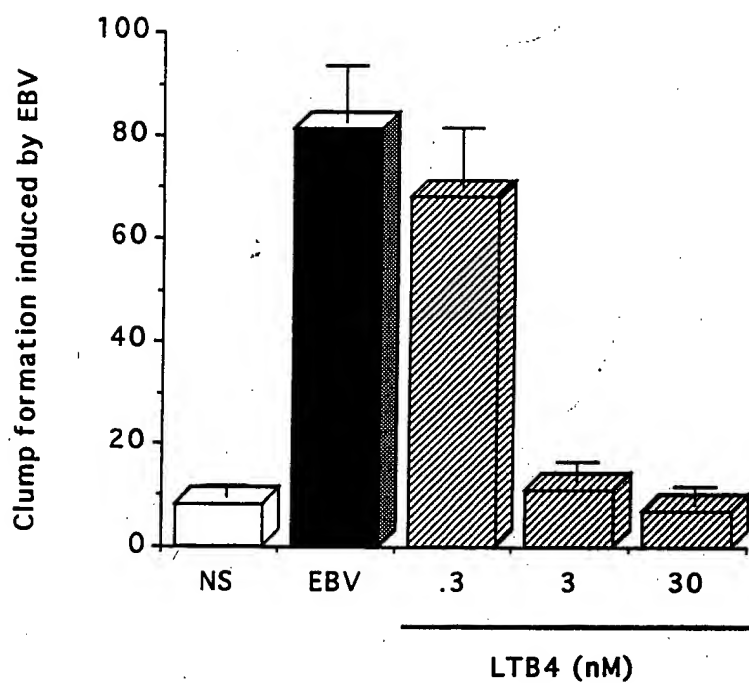


Fig. 1C

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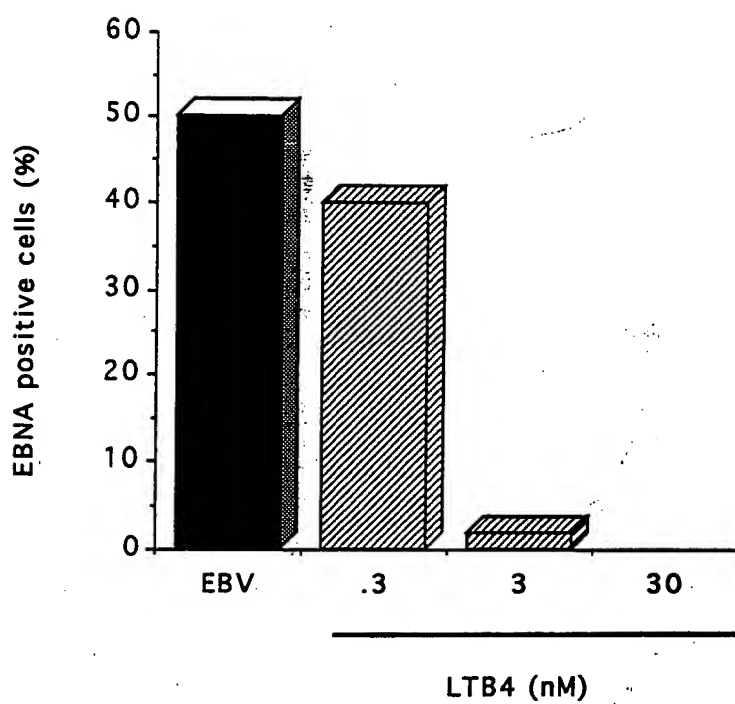


Fig. 2A

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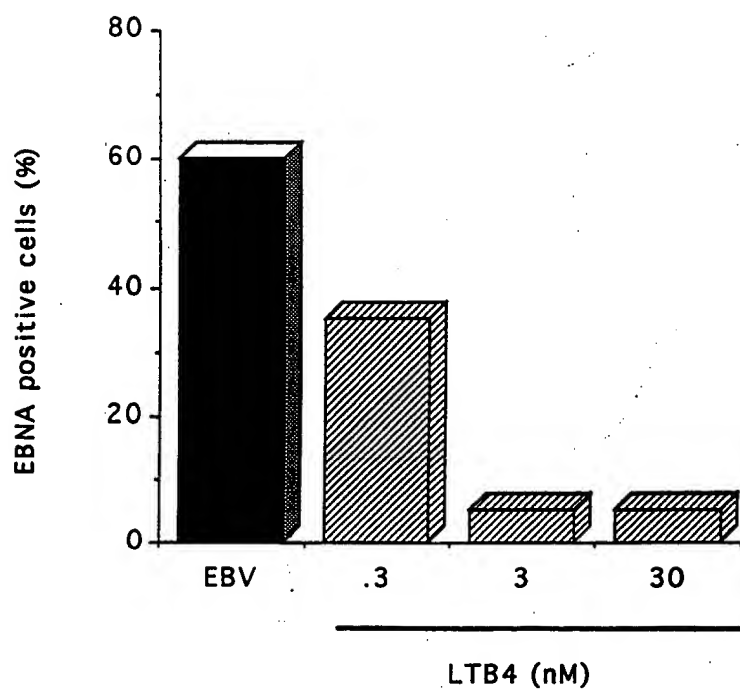


Fig. 2B

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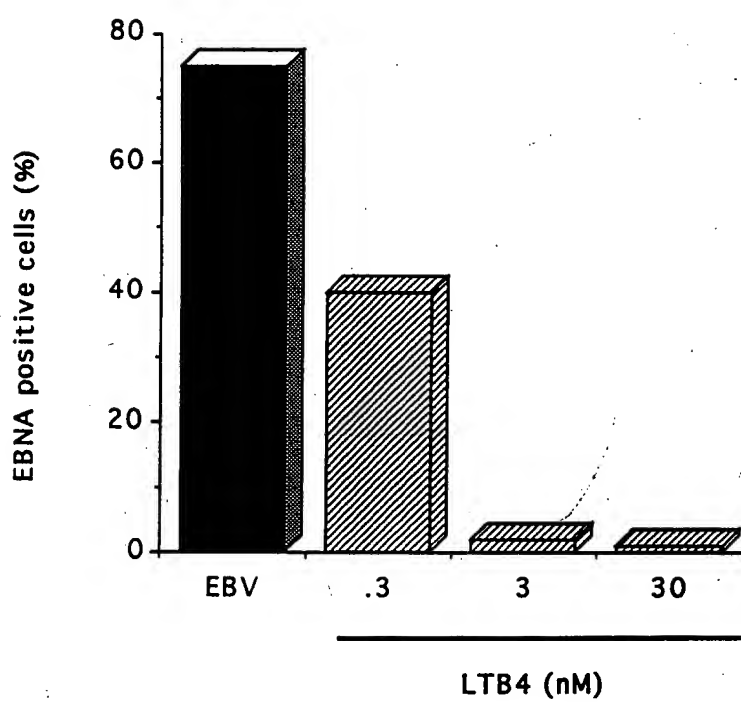


Fig. 2C

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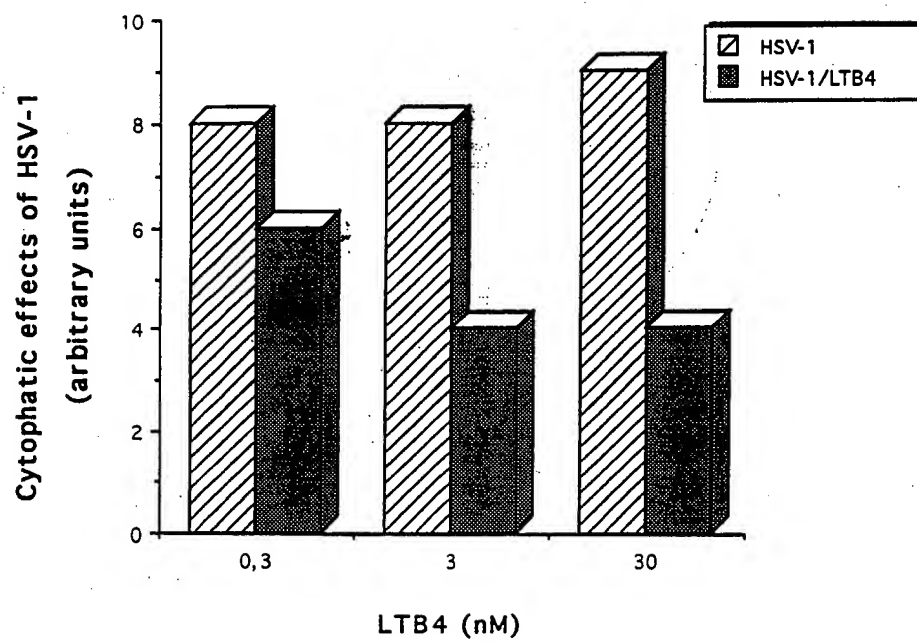


Fig. 3

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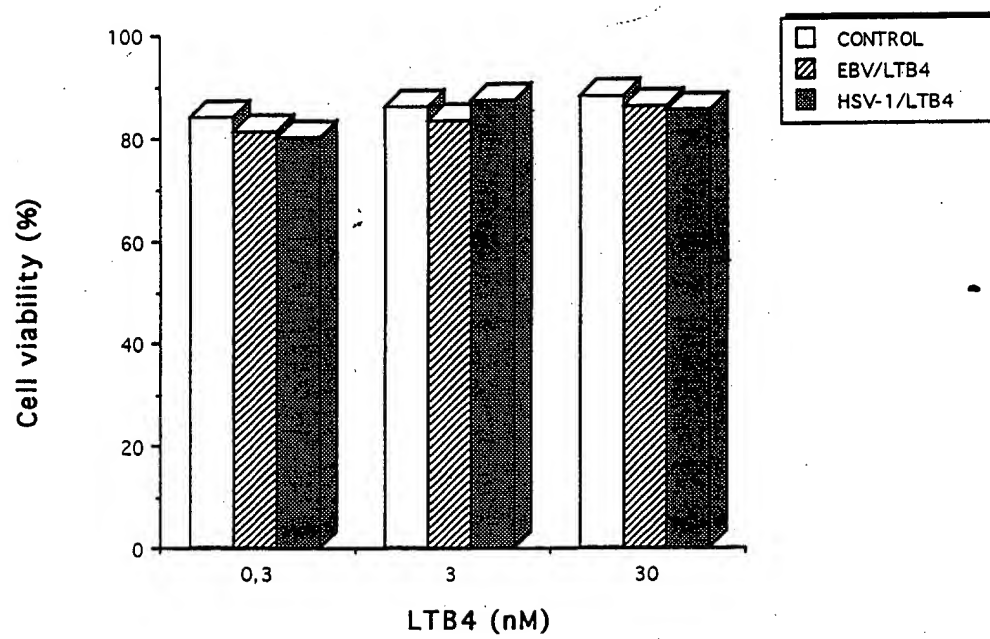


Fig. 4

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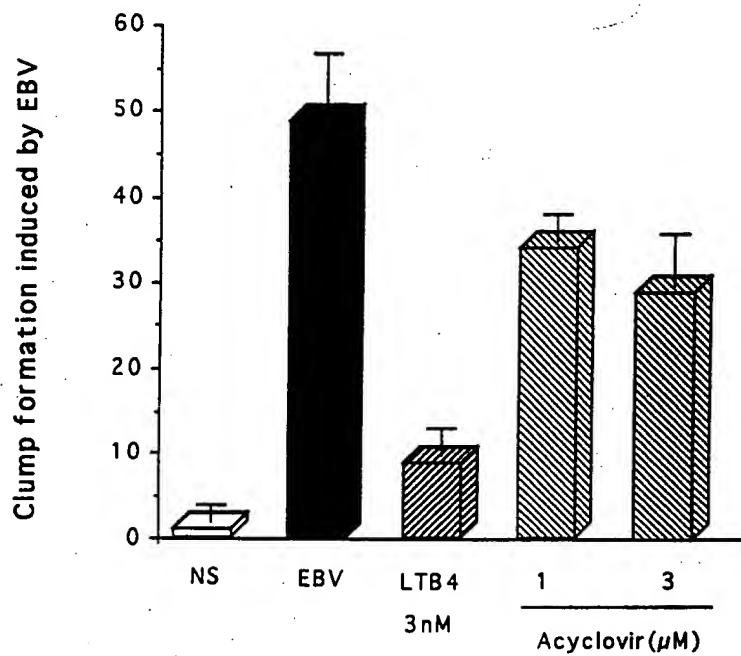


Fig. 5A

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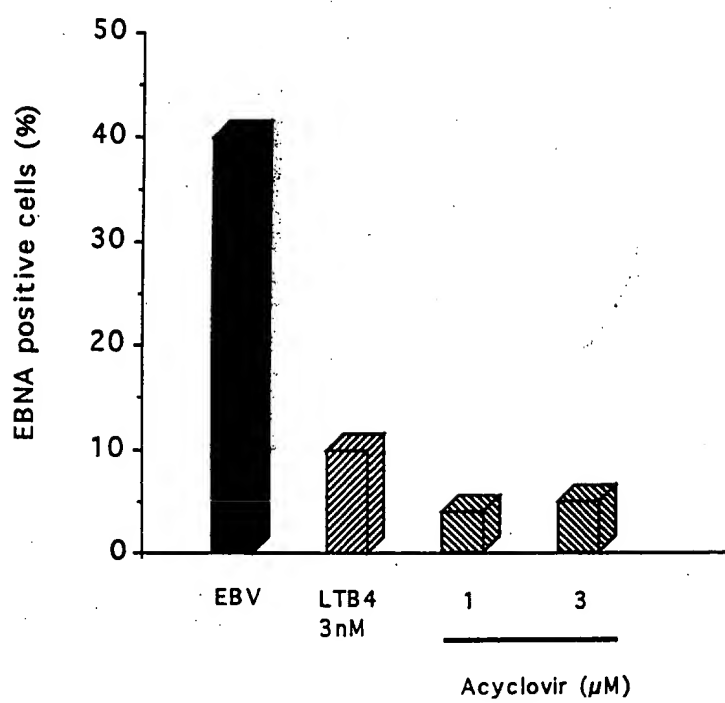


Fig. 5B